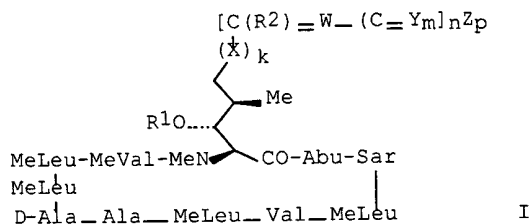


L35 ANSWER 233 OF 272 HCAPLUS COPYRIGHT 2006 ACS on STN  
ACCESSION NUMBER: 1989:527017 HCAPLUS Full-text  
DOCUMENT NUMBER: 111:127017  
TITLE: Fluorescence polarization immunoassay for cyclosporin  
A and metabolites based on novel cyclosporin A  
derivatives  
INVENTOR(S): Wang, Nai Yi; Wang, Philip P.; Morrison, Marjorie Anne  
PATENT ASSIGNEE(S): Abbott Laboratories, USA  
SOURCE: Eur. Pat. Appl., 17 pp.  
CODEN: EPXXDW  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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EP 283801	A2	19880928	EP 1988-103397	19880304
EP 283801	A3	19900530		
R: BE, CH, DE, ES, FR, GB, IT, LI				
JP 63258491	A2	19881025	JP 1988-73057	19880325
CA 1341463	A1	20041102	CA 1988-562525	19880325
US 5239057	A	19930824	US 1991-776890	19911015
US 5427960	A	19950627	US 1994-318570	19941005
PRIORITY APPLN. INFO.:			US 1987-31494	A 19870327
			US 1989-376244	B1 19890706
			US 1991-776890	A3 19911015
			US 1993-60598	B1 19930512
OTHER SOURCE(S):		MARPAT 111:127017		
GI				



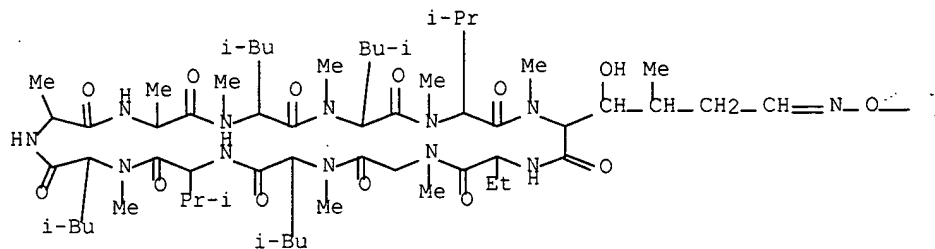
AB A method is described for prepn. of cyclosporin A derivs. I [k = 0-1 (k = 0 only if n = 1); m = 0-2; n, p = 0-1; R1 = H or a protecting group; R2 = H, lower alkyl, or CH(OH)Me; W = 1-20 (not including H) atoms of C, N, O, S, with ≤2 heteroatoms bonded together and with O never bonded to O or S; X = CH2, CHOH, C(O) (n = 0), or CH2OH (p = 0); Y = O, S, or NH; Z = a poly(amino acid), a poly(amino acid) derivative, a fluorescent moiety, OH, NH2, NHH2, ORa, SRa, NHRa, NRaRb (Ra, Rb = stable C1-10 chain), SH, or a leaving group; MeVal, MeLeu, Sar, and Abu represent residues of N-methylvaline, N-methylleucine, sarcosine, and L-α-aminobutyric acid, resp.]. The derivs. are used as (1) immunogens in formation of antibodies specific to cyclosporin A and some metabolites, and (2) precursors in synthesis of fluorescent tracers having ≥1 epitope in common with cyclosporin A and some metabolites. Antibodies and tracers are employed in a fluorescence polarization immunoassay (FPIA) for cyclosporin A and metabolites in biol. fluids. [6-(Carboxymethyloximino)-3-(R)-hydroxy-4-(R)-methyl-2-(S)-methylaminohexanoyl]6cyclosporin A (I; k = 0; m, n, p = 1; R1, R2 = H; W = NOCH2; Y = O; Z = OH) (preparation given) was conjugated to bovine serum albumin with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl, and the resulting immunogen was used to immunize exptl. animals. A fluorescent cyclosporin A tracer was prepared from [7-carboxy-3-(R)-hydroxy-4-(R)-methyl-2-(S)-methylamino-6-heptenoyl]6cyclosporin A (I; k = 0; m, n, p = 1; R2 = H; W = CH; Y = O; Z = OH) and aminomethylfluorescein-HCl. To serum or plasma samples was added precipitation reagent (30 mM NH4OAc in 98.5% aqueous Me2CHOH). Following mixing and centrifuging, samples were analyzed with an automated assay employing an Abbott TDx Analyzer and a Cyclosporin and Metabolites Reagent pack. FPIA sensitivity was 15 ng/mL for cyclosporin A and metabolites. In a comparison of 208 clin. samples against an available RIA, linear regression anal. gave a slope of 1.153, an intercept of 21.06, and a correlation coefficient of 0.813.

IT **122547-79-9P**

RL: SPN (Synthetic preparation); PREP (Preparation)  
 (preparation and conjugation with albumin)

RN 122547-79-9 HCAPLUS

CN Cyclosporin A, 6-[(3R,4R)-6-[(carboxymethoxy)imino]-3-hydroxy-N,4-dimethyl-L-norleucine]- (9CI) (CA INDEX NAME)



—CH<sub>2</sub>—CO<sub>2</sub>H

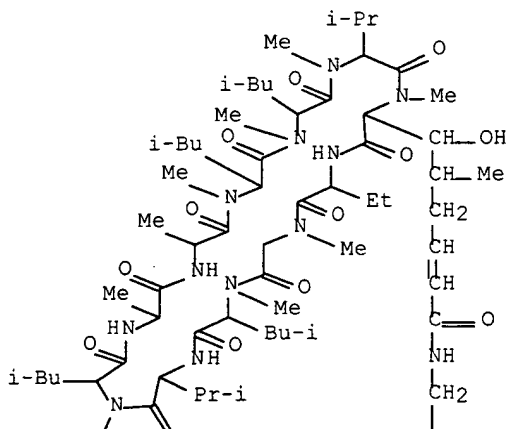
IT 122575-49-9P

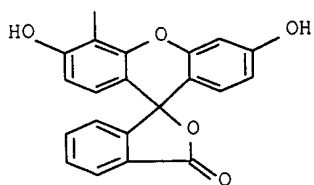
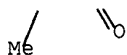
RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of, for fluorescence polarization immunoassay for cyclosporin A)

RN 122575-49-9 HCAPLUS

CN Cyclosporin A, 6-[(3R,4R)-6,7-didehydro-3-hydroxy-8-[[[(6'-hydroxy-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthen]-3'-yl)oxy]methyl]amino]-N,4-dimethyl-8-oxo-L-2-amino-octanoic acid]- (9CI) (CA INDEX NAME)





IT 121584-52-9P 122547-77-7P 122547-78-8P  
122547-80-2P 122547-81-3P 122547-82-4P  
122547-83-5P

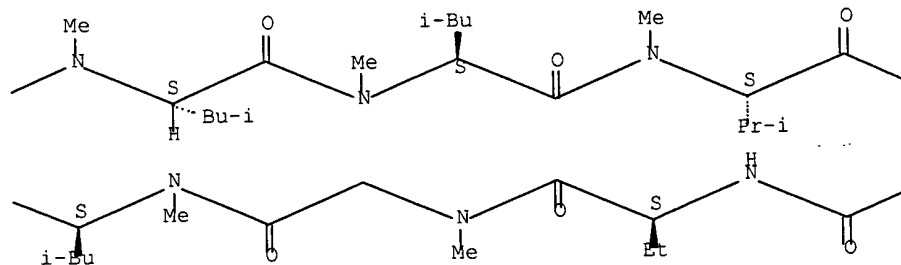
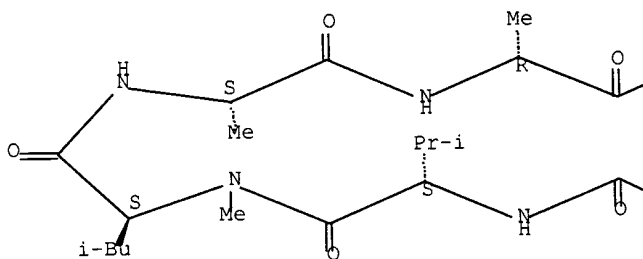
RL: SPN (Synthetic preparation); PREP (Preparation)

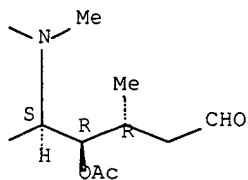
(preparation of, in albumin-cyclosporin A derivative conjugate preparation)

RN 121584-52-9 HCAPLUS

CN Cyclosporin A, 6-[(3R,4R)-3-(acetyloxy)-N,4-dimethyl-6-oxo-L-norleucine]-  
 (9CI) (CA INDEX NAME)

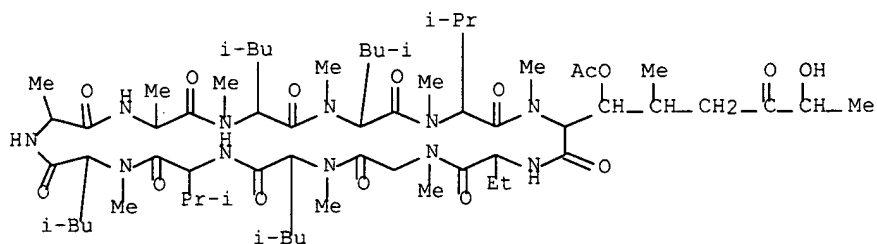
Absolute stereochemistry. Rotation (-).





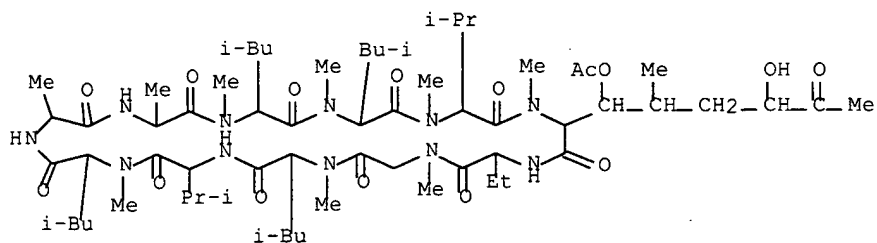
RN 122547-77-7 HCAPLUS

CN Cyclosporin A, 6-[(3R,4R)-3-(acetyloxy)-7-hydroxy-N,4-dimethyl-6-oxo-L-2-aminooctanoic acid]- (9CI) (CA INDEX NAME)



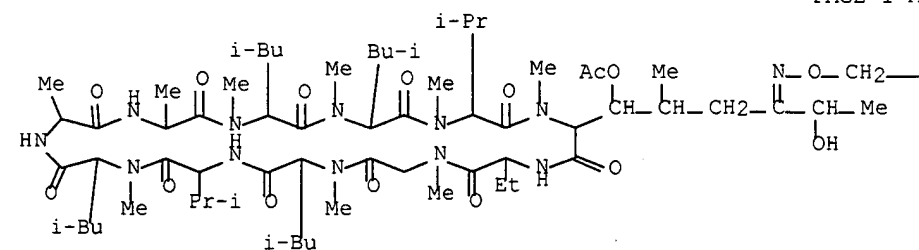
RN 122547-78-8 HCAPLUS

CN Cyclosporin A, 6-[(3R,4R)-3-(acetyloxy)-6-hydroxy-N,4-dimethyl-7-oxo-L-2-aminooctanoic acid]- (9CI) (CA INDEX NAME)

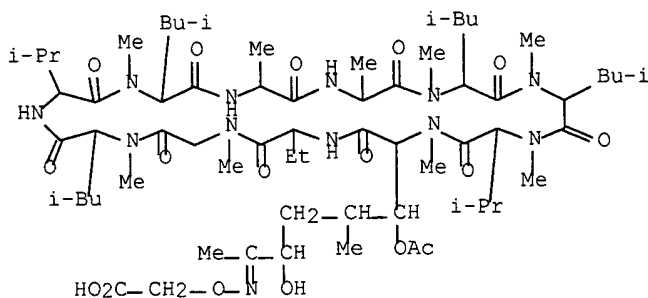


RN 122547-80-2 HCAPLUS

CN Cyclosporin A, 6-[(3R,4R)-3-(acetyloxy)-6-[(carboxymethoxy)imino]-7-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI) (CA INDEX NAME)



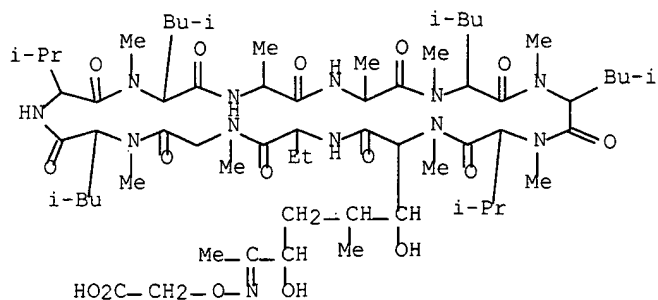
CN Cyclosporin A, 6-[(3R,4R)-3-(acetyloxy)-7-[(carboxymethoxy)imino]-6-hydroxy-N,4-dimethyl-L-2-aminooctanoic acid]- (9CI) (CA INDEX NAME)



CN Cyclosporin A, 6-[(3R,4R)-6-[(carboxymethoxy)imino]-3,7-dihydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-(9CI) (CA INDEX NAME)

[illegible]
$$\text{---CO}_2\text{H}$$

CN	Cyclosporin A, 6-[(3R,4R)-7-[(carboxymethoxy)imino]-3,6-dihydroxy-N,4-dimethyl-L-2-aminooctanoic acid]-(9CI) (CA INDEX NAME)
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IT 100364-58-7P 122547-84-6P 122547-85-7P

RL: SPN (Synthetic preparation); PREP (Preparation)

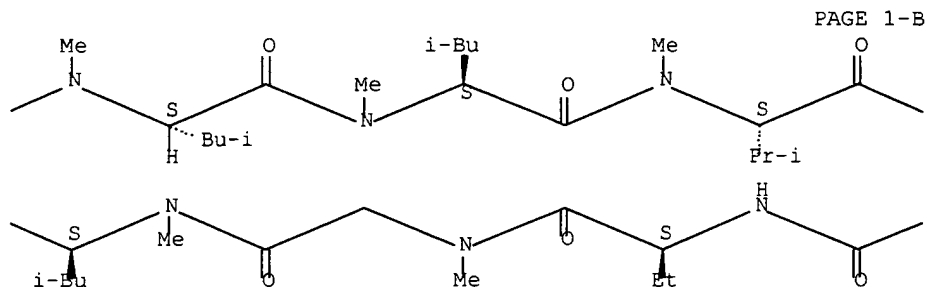
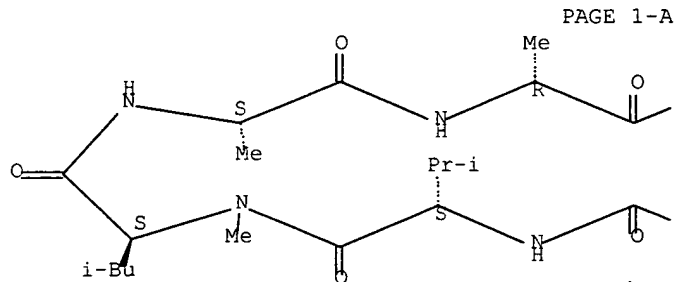
(preparation of, in cyclosporin A-aminomethylfluorescein conjugate preparation)

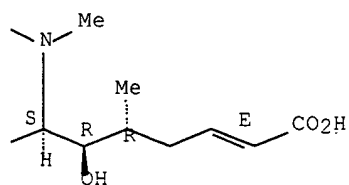
RN 100364-58-7 HCAPLUS

CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

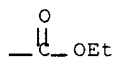
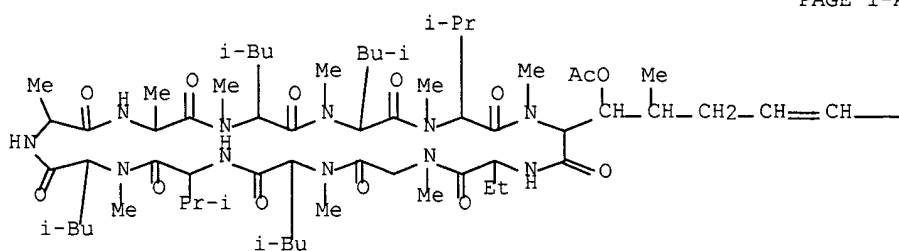
Double bond geometry as shown.





RN 122547-84-6 HCAPLUS

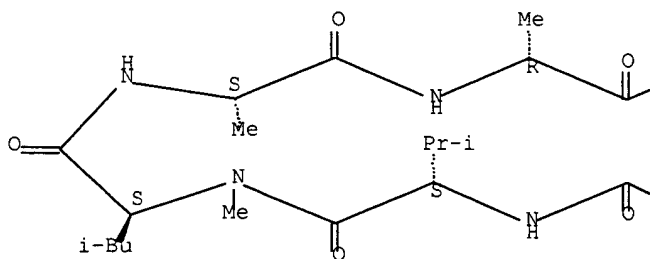
CN Cyclosporin A, 6-[(3R,4R)-3-(acetyloxy)-6,7-didehydro-8-ethoxy-N,4-dimethyl-8-oxo-L-2-aminooctanoic acid]- (9CI) (CA INDEX NAME)



RN 122547-85-7 HCAPLUS

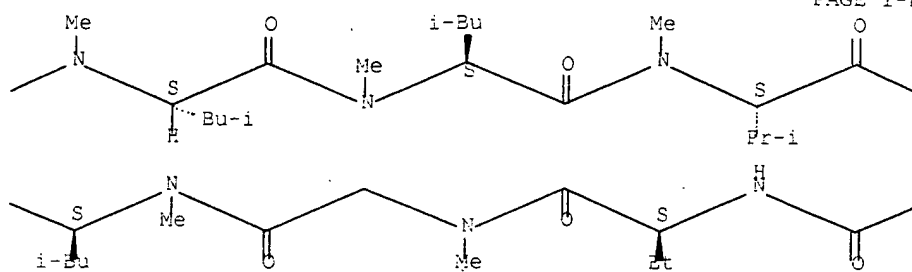
CN Cyclosporin A, 6-[(2E,5R,6R,7S)-6-hydroxy-5-methyl-7-(methylamino)-2-octenedioic acid]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
Double bond geometry as shown.

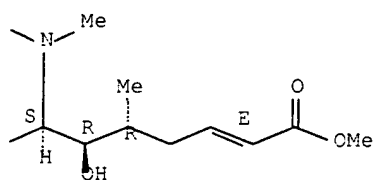




PAGE 1-B



PAGE 1-C



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